Merck & Co., Inc.
West Point PA 19486

January 6, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

[Docket No. 00D-0186] International Conference on Harmonization; Guidance on M4 Common Technical Document; REFERENCE: M4E: CTD - Efficacy

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's research has produced many of the most important pharmaceutical products on the market today.

Merck has participated with health authorities and industry scientists from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). Merck continues to support the objectives of ICH: to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical and biological products caused by incompatible regulatory schemes.

In the course of bringing Merck's product candidates through developmental testing and clinical trials to the market, Merck has filed numerous original and supplemental New Drug Applications (NDAs) and Biological License Applications (BLAs). Merck typically prepares a single Worldwide Marketing Application (WMA) which is filed electronically and, less often, filed on paper, in most countries in the world, simultaneously. Therefore, we are very interested in this *ICH Guidance on M4 Common Technical Document* and well qualified to comment on it.

Although all ICH participants have valiantly pursued harmonization of documentation for marketing applications, this FDA version of the M4 Common Technical Document (CTD), specifically the *M4E: CTD - Efficacy* guidance differs from the European *Notice To Applicant's* with regard to the same information, in a way that is fairly significant. Indeed, this one instance of *lack* of harmonization is precisely an example of regional distinctions that have been considered unjustified and unnecessary and, therefore, eliminated during the ICH process.

The numbering/indexing systems used by the US FDA and by the European authorities, when more than one indication is submitted for a single product in one marketing application, are not harmonized and will require regional manipulation that should not be necessary.

FDA's Guidance for Industry M4E: CTD -- Efficacy, Module 2 - Section 2.7.3 Summary of Clinical Efficacy (page 22) reads:

> "A separate Section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 2.7.3 is submitted, the sections should be labeled by indication (e.g., 2.7.3 pneumonia, 2.7.3 URI)".

In contrast, the European *Notice to Applicants (NTA)* provides the following instructions for the same information in Module 2 - Section 2.7.3 Summary of Clinical Efficacy (page 139 of 165):

> "A separate Section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 2.7.3 is submitted, the sections should be labeled 2.7.3A, 2.7.3B, 2.7.3C".

As noted above, Merck, as many other global companies, prepares one Worldwide Marketing Application (WMA) to file simultaneously in many countries. This difference in the numbering systems between the US and Europe will require that one WMA be created for filing in one geographic area, then, altered for filing in the other region, thereby prohibiting simultaneous filings. This unique numbering sytem will equally affect both paper filings and electronic.

This difference in numbering systems is not included in Module 1 where regional distinctions are noted, and rightly so. At the same time, we understand that other numbering and indexing systems have been harmonized to avoid similar problems. Therefore, we must conclude that this difference is an oversight and we bring it to your attention in the interest of clarity and cooperation.

We welcome the opportunity to provide feedback on *ICH Guidance on M4 Common Technical Document* and, if appropriate, we would be pleased to meet with you to discuss this issue.

Sincerely,

Bonnie J. Goldmann, MD
Vice President
Regulatory Affairs-US

Henrietta N. Ukwu, MD, FACP
Vice President
Worldwide Regulatory Affairs
Vaccines/Biologics

remely Urgent:
ent please hand deliver to
ssee.

☐ **FedEx Priority Overnight®** Next business morning service (not available to all locations).

☐ **FedEx Standard Overnight®** Next business day service (not available to all locations).

☐ **FedEx First Overnight℠** Earliest next business morning delivery to select locations

☐ **FedEx International Services** Scheduled delivery times vary by location.

☐ **Saturday D** Service not ava locations.

PRIORITY OVERNIGHT MON

FedEx.
emp# 183993 11JAN02
TRK# 8331 4325 1819 FORM

Deliver By:
14JAN02
A2

IAD

20852 -MD-US ZM GAIA

FedEx® Letter
Federal Express

Limitation on Contents

Maximum eight pages. If envelope, ar rate will app
Contents must l w it to be equivalents x Letter.

Declared Value/

Address/

Use the U.S. Ai Alaska, ar
Use the Inter to/from Puerto R
Use street addr U.S. Zip Codes addresses and tele

FedEx Express USA Airbill

FedEx Tracking Number 833143251819

Form I.D. No. 0200 Recipient's Copy

1 From
Date 11/11/02
Sender's Name DR. B. Goldmann Phone 484 344-2919
Company Merck & Co.
Address 5 Sentry East Parkway Dept./Floor/Suite/Room
City Blue Bell State PA ZIP 19422

2 Your Internal Billing Reference 57834-774t-040

3 To
Recipient's Name Dockets Management Branch (HFA-305 Phone
Company Food & Drug Admin.
5630 Fishers Lane
Ex location, print FedEx address. We cannot deliver to P.O. boxes or P.O. ZIP codes.
Room 1061 Dept./Floor/Suite/Room
City Rockville State MD ZIP 20852

833143251819

4a Express Package Service *Packages up to 150 lbs.* Delivery commitment may be later in some areas.
- [X] FedEx Priority Overnight — Next business morning
- [ ] FedEx Standard Overnight — Next business afternoon
- [ ] FedEx First Overnight — Earliest next business morning delivery to select locations
- [ ] FedEx 2Day — Second business day
- [ ] FedEx Express Saver — Third business day

FedEx Envelope rate not available. Minimum charge: One-pound rate

4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas.
- [ ] FedEx 1Day Freight* — Next business day
- [ ] FedEx 2Day Freight — Second business day
- [ ] FedEx 3Day Freight — Third business day

* Call for Confirmation

5 Packaging * Declared value limit $500
- [X] FedEx Envelope*
- [ ] FedEx Pak* — Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
- [ ] Other

6 Special Handling Include FedEx address in Section 3.
- [ ] SATURDAY Delivery — Available only for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
- [ ] HOLD Weekday at FedEx Location — Not available for FedEx First Overnight
- [ ] HOLD Saturday at FedEx Location — Available only for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.
- [ ] No
- [ ] Yes — As per attached Shipper's Declaration
- [ ] Yes — Shipper's Declaration not required
- [ ] Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg

Dangerous Goods (including Dry Ice) cannot be shipped in FedEx packaging.
- [ ] Cargo Aircraft Only

7 Payment *Bill to:* Enter FedEx Acct. No. or Credit Card No. below.
- [X] Sender — Acct. No. in Section 1 will be billed.
- [ ] Recipient
- [ ] Third Party
- [ ] Credit Card
- [ ] Cash/Check
- [ ] Obtain Recip. Acct. No.

Total Packages	Total Weight	Total Declared Value†	Total Charges
1		$ .00	Credit Card Auth.

†Our liability is limited to $100 unless you declare a higher value. See back for details.

8 Release Signature *Sign to authorize delivery without obtaining signature.*

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

Questions? Visit our Web site at fedex.com or call 1.800.Go.FedEx® 800.463.3339.

Rev. Date 10/01 • Part #157612 • ©1994–2001 FedEx • PRINTED IN U.S.A. SBFE 12/01

446

FDA
THIS PACKAGE HAS BEEN X-RAYED